REMARKS

The Examiner's Office Action of April 19, 2004 has been received and carefully reviewed. By this amendment, Applicant amends the specification to include the address of the German Collection of Microorganisms and Cell Cultures, the depository with which the biological material identified under accession numbers DSM ACC 2355, DSM ACC 2356, DSM ACC 2360 and DSM ACC 2362 were made. Claims 54-91 are pending in the application. A Notice of Appeal was filed on September 20, 2004.

I. Rejection of Claims 54-91 Under 35 U.S.C. 112, first paragraph

The Examiner has maintained the rejection of claims 1-4 and 13-14, as now applied to new claims 54-91, under 35 U.S.C. 112, first paragraph, on the basis that the claims contain subject matter which is not described in the specification in such a way to enable one skilled in the art to which it pertains, or with which is most clearly connected, to make and/or use the invention. For the following reasons, Applicant believes that because there is sufficient guidance in the specification to enable one of ordinary skill to make and use the invention, and that this rejection should, therefore, be withdrawn.

Independent claim 54 is directed to a method for detecting an infection of an acid-resistant microorganism, comprising:

(a) incubating a stool sample of the mammal with at least two different monoclonal antibodies, fragments, or derivatives thereof under conditions allowing formation of complexes between antigens from the acid-resistant microorganism and the antibodies, fragments or derivatives thereof, in which

(aa) a first monoclonal antibody or fragment or derivative thereof specifically binds an epitope of a first antigen, which shows at least with some mammals a structure after intestinal passage that corresponds to a native structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid-resistent microorganism, an extract or lysate thereof, protein therefrom, a fragment thereof or synthetic peptide;

(ab) a second monoclonal antibody or fragment or derivative thereof specifically binds an epitope of a second antigen, differing from the epitope of the first antigen, which

shows at least with some mammals a structure after intestinal passage that corresponds to the native structure, or a structure which a mammal produce antibodies against after being infected or immunized with the acid-resistant microorganism, an extract or lysate thereof, a protein therefrom, a fragment thereof or a synthetic peptide, in which the groups of mammals according to (aa) and (ab) may overlap, and in total make up the overall number of infected mammals; and

(b) detecting the formation of at least one antigen-antibody complex according to (aa) or (ab).

Claims 55-76 depend on independent claim 1, either directly or indirectly.

Independent claim 77 is directed to a method for detecting an infection with *Helibactor pylori* in the stool of a mammal comprising:

(a) incubating a stool sample with at least two different monoclonal antibodies, fragments or derivatives thereof under conditions allowing antigen-antibody complex formation, in which

(aa) a first monoclonal antibody, fragment or derivative thereof specifically binds ß-urease or a fragment thereof;

(ab) a second monoclonal antibody, fragment or derivative thereof specifically binds the 26kDa-antigen or a fragment thereof or specifically binds Hsp60 or a fragment thereof, and

(b) detecting the formation thereof of at least one antigen-antibody complex as set out in (aa) or (ab).

Claims 78-91 depend from claim 77, either directly or indirectly.

The Examiner argues, with respect to the limitation "specifically binds to an epitope of a first antigen" and "specifically binds an epitope of a second antigen," that, without guidance as to what the structure of the immunogen looks like, one of ordinary skill in the art would be hard pressed to determine which antibodies are capable of specifically binding an undisclosed structure. The Examiner further argues that the claims recite "derivatives" which allow for multiple amino acid substitutions, insertions and deletions within the epitope of undefined structure. The Examiner concludes, therefore, that "in view of the lack of guidance, lack of examples, and lack of predictability associated with regarding to producing and using a myriad of derivatives encompassed in

the scope of the claims one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention."

Applicant reiterates that the claimed invention provides a method for reliably detecting an infection of an acid-resistant microorganism, particularly, *Helicobacter pylori*, in the stool by using at least two monoclonal or fragements or derivatives thereof. The monoclonal antibodies or fragments or derivatives used to bind to two different epitopes greatly improves the reliability of the test. Antibodies and fragments or derivatives thereof which are useful for the method of the present invention can be obtained by a new approach which has not been used in the past.

In the past, a lysate of microorganisms was used to prepare polyclonal antibodies and the antiserum was used because it was not deemed possible to use monoclonal antibodies to get sufficient efficiency and specificity. The inventors of the claimed invention, however, have found that by using at least two monoclonal antibodies which bind to different epitopes on different antigens on the one hand, and by using those antibodies which bind to epitopes that have survived the intestine on the other hand, it is possible to provide a sensitive and reliable test method, as presently claimed. The important information which is given by the present application, therefore, is the finding that using two different monoclonal antibodies results in a reliable test as soon as those antibodies can bind to epitopes surviving the intestine. The examples set forth in the written description, especially Examples 1 to 4, adequately teach one of ordinary skill how to raise the monoclonal antibodies which can selectively bind to epitopes present in stool sample, and which survive the intestine.

Further, Applicant notes that independent claim 54 does not simply recite an "epitope of a first antigen" and an "epitope of a second antigen," but requires that the related epitopes show "a structure after intestinal passage that corresponds to a native structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism, an extract or lysate thereof, protein therefrom, a fragment thereof or synthetic peptide." As defined in the specification,

> [T]he term "shows [...] a structure after the intestinal passage that corresponds to the native structure" means that the epitope of an antigen is recognized after the intestinal passage by a monoclonal antibody, derivative or fragment thereof or the aptamer, which has been obtained against or which is bound to the same antigen/epitope that has not passed the intestinal

> passage. In other words, the epitipe/antigen that is specifically bound by said antibody or fragment or derivative thereof has passed the intestinal passage intact or almost intact as regards its structure and has not been degraded. A source for the native structure of the epitope/antigen may, for instance, be a bacterial extract that was disrupted with a French press and further purified according to standards (cf. Sambrook et al. "Molecular Cloning, A Laboratory Manual", 2nd edition 1989, CHS Press, Cold Spring Harbor, USA), or a lysate which has been further purified according to the standard methods (e.g., Sambrook et al, ibid).
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> [T]he term "show [...] a structure after the intestinal passage that corresponds to [...] the structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism or an extract or lysate thereof or a protein therefrom or a fragment thereof or a synethetic peptide" means according to the invention that the epitope recognized by the monoclonal antibody, fragment, derivative or aptamer corresponds to an epitope that is presented by the immune system of a mammal, preferably a human. The mechanisms of antigen presentation as well as the mechanisms leading to the processing of antigens and the variety of antibodies resulting therefrom has been known to the prior art and has been described, for instance, in Janeway and Travers, Immunologie, 2nd edition 1997, Spektrum Akademischer Verlag GmbH, Heidelberg. These epitopes may differ from native epitopes.

See, Specification, page 8, pgh. 2 – page 9, pgh. 1.

In a preferred embodiment, the acid-resistant microorganism is a bacterium, especially *Helicobacter pylori*, *Helicobacter hepaticus* or *Mycobacterium tuberculoses* or *Campylobacter pylori*; and it is preferred that the two epitopes are epitopes of a urease and a heat shock protein, preferably Hsp60, of an alkylhydroperoxide-reductase, preferably of the 25kDa protein, the 20kDa-protein (3-dehydro-quinase, type II), of the 16.9 kDA-protein (neutrophil-activating protein) or of the 38 kDa-protein (fructose-bisphosphate aldolase). *See,* Specification page 2, pgh 1.

Moreover, with respect to independent claim 77, Applicant notes that claim 77 does note recite the claim language "an epitope of a first antigen" or "an epitope of a second antigen." Rather, claim 77 recites "ß-urease or a fragment thereof" as the epitope to which the first monoclonal antibody of the claim method specifically binds, and "the 16kDa-antigen or a fragment thereof" or "Hsp60 or a fragment thereof," as the epitope to which the recited monoclonal antibody specifically binds.

Thus, contrary to the Examiner's contention, undue experimentation is not

necessary to practice the method of claim 54-91. Those of skill in the art are clearl / capable of determining if a particular epitope shows a structure after intestinal passage tha1 corresponds to a native structure through tests know to those of ordinary skill, incl ding those described. Accordingly, Applicant respectfully submits that the Examiner's rejection of these claims 54-91 under 35 U.S.C. 112, first paragraph, should with reconsidered and withdrawn.

Further, regarding the term "monoclonal antibodies or fragments or derivatives thereof," Applicant submits that the written description is also fully enabling for this term, as it will be apparent to one of one of ordinary skill the finding fragments and derivatives can be found by simply screening for those fragments and derivatives which bind to those epitopes which the complete antibodies bind. As defined in the specification,

> [T]he terms "fragments" or derivatives" of monoclonal antibodies have the same binding specificity as monoclonal antibodies. Such fragments or derivatives may be produced according to common techniques, e.g. Harlow and Lane Antibodies, A Laboratory Manual," CSH Press, Cold Spring Harbor, USA, 1988. Examples of fragments are Fab-, F(ab')$_2$ or Fv-fragments. Examples of derivatives are scFv-fragments. Derivatives may also be substances which have been produced chemically and which have the same or improved binding properties as the antibodies. Such substances may be produced for instance by peptidomimetics or various rounds of phage display and subsequent selection as to improved binding properties.

See, Specification, page 7, pgh 3.

Independent claims 54 and 77 require that only those monoclonal antibodies or fragments or derivatives thereof are used which can bind specifically to an epitope of an antigen which has survived the intestine. Accordingly, since the claimed language "epitope of a first antigen" and "epitope of a second antigen" is enabled for the reasons discussed above, the term "monoclonal antibody or fragments or derivative thereof" is likewise enabled. No single amino acid, debris or parts of an antibody which cannot bind with epitopes in a stool sample are claimed because they will not bind specifically. Thus, it can be found by only few routine tests if an antibody, a fragment or derivative thereof is able to bind and, thus, can be used in the present invention. Summarizing, the description of the present application gives enough guidance to the skilled artisan to find further antibodies, fragments and derivatives which are useful for the present method

With respect to the Examiner's statement that that "derivatives" which allow for multiple amino acid substitution, insertions and deletions with this epitope of undefined structure," Applicant believes there is a misunderstanding. It seems that the Examiner has mistakingly started from the assumption that one has to know the structure of the epitope to find the correct antibody. Applicant respectfully notes, however, that this was the approach which was used in the prior art and it was the surprising idea of the present inventors not only to search for the epitopes but to look for specific binding. Contrary to the Examiner's understanding, the epitopes which shall be determined are present in the stool sample and are not processed to derivatives or fragments. The derivatives or fragments are derived from antibodies and the skilled artisan is well aware of methods how to prepare derivatives and fragments of antibodies and to find those fragments and derivatives which specifically bind an epitope. Moreover, the term "derivative" has a clear meaning in the art of antibodies and one or ordinary skill in the art will immediately know who to find a derivative of an antibody and at the same time has guidance in the application on how to find a useful derivative.

Claims 64, 67, 73, 80, 83 and 87 have further been rejected under 35 U.S.C. 112, first paragraph, on the basis that the specification fails to provide an enabling disclosure without complete evidence that the claimed biological materials are known and readily available to the public. In particular, it is stated that the specification lacks complete deposit information for the deposit of DSM ACC 2355, DSM ACC 2356, DSM ACC 2362, and DSM ACC 2362. Applicant assumes that the duplicate reference to DSM ACC 2362 is a typographical error, and that the Examiner intended to state DSM ACC2360, the fourth accession number referenced on page 15 of the specification. As evidence that the requisite deposits were made, Applicant submits herewith a copy of the deposit receipts relative to each these accession numbers. These deposit receipts were earlier filed with Applicant's Preliminary Amendment dated January 1, 2003. To comply with the requirements of 37 C.F.R. 1.809, the specification is herein amended to identify the address of the depositary with which the biological deposits were made. All restrictions upon public access to the deposit to the deposit will be irrevocably removed upon the grant of a patent on this application and the deposit will be replaced if viable samples cannot be dispensed by the depositary.

In view of the foregoing, it is respectfully submitted that new independent claims 54 and 77 satisfy the requirements of 35 U.S.C. 112, first paragraph. Accordingly, it is

respectfully requested that the Examiner's rejection to the subject matter of these claims be reconsidered and withdrawn. Inasmuch as the foregoing arguments apply to claims 55-76 and 79-91 by virtue of their dependency on independent claims 54 and 77, respectively, it is respectfully submitted that the Examiner's rejection to the subject matter of these claims also be reconsidered and withdrawn.

Accordingly, it is respectfully submitted that the Examiner's rejection under 35 U.S.C. 112, second paragraph is improper. Reconsideration and withdrawal of this rejection is respectfully requested.

II. Rejection of Claims 54-91 under 35 U.S.C. 112, first paragraph

The rejection of claims 1-4 and 13-14 under 35 U.S.C. 112, first paragraph has been maintained, as applied to newly added claims 54-91. In particular, these claims are rejected on the basis of being directed to methods for detecting an infection of an acid-resistant microorganism in the stool wherein the monoclonal antibody specifically binds an "epitope of the first antigen," and specifically binds "an epitope of a second antigen." The Examiner, referencing the claim language which recites "an epitope of an antigen," contends that trying to determine which epitope of the undefined structure is referred to would require excessive experimentation. In support of this contention, the Examiner cites the teachings of U.S. Patent No. 4,879,212 to Fox, which sets forth that "short linear polypeptides often appear not to have the ability to mimic the required secondary and tertiary conformational structures to constitute appropriate immunogenic and antigenic determinants. According to the Examiner, this is directly analogous to Applicant's claim to an "epitope" of an antigen. Applicant respectfully disagrees.

As discussed above, applicant notes that independent claim 54 does not simply recite an "epitope of a first antigen" and an "epitope of a second antigen," but requires that the recited epitopes show "a structure after intestinal passage that corresponds to a native structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism, an extract or lysate thereof, protein therefrom, a fragment thereof or synthetic peptide." As defined in the specification,

> [T]he term "shows [...] a structure after the intestinal passage that corresponds to the native structure" means that the epitope of an antigen is recognized after the intestinal passage by a monoclonal antibody, derivative

> or fragment thereof or the aptamer, which has been obtained against or which is bound to the same antigen/epitope that has not passed the intestinal passage. In other words, the epitipe/antigen that is specifically bound by said antibody or fragment or derivative thereof has passed the intestinal passage intact or almost intact as regards its structure and has not been degraded. A source for the native structure of the epitope/antigen may, for instance, be a bacterial extract that was disrupted with a French press and further purified according to standards (cf. Sambrook et al. "Molecular Cloning, A Laboratory Manual", 2nd edition 1989, CHS Press, Cold Spring Harbor, USA), or a lysate which has been further purified according to the standard methods (e.g., Sambrook et al, ibid).
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> [T]he term "show [...] a structure after the intestinal passage that corresponds to [...] the structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism or an extract or lysate thereof or a protein therefrom or a fragment thereof or a synethetic peptide" means according to the invention that the epitope recognized by the monoclonal antibody, fragment, derivative or aptamer corresponds to an epitope that is presented by the immune system of a mammal, preferably a human. The mechanisms of antigen presentation as well as the mechanisms leading to the processing of antigens and the variety of antibodies resulting therefrom has been known to the prior art and has been described, for instance, in Janeway and Travers, Immunologie, 2nd edition 1997, Spektrum Akademischer Verlag GmbH, Heidelberg. These epitopes may differ from native epitopes.

See, Specification, page 8, pgh. 2 – page 9, pgh. 1.

In a preferred embodiment, the acid-resistant microorganism is a bacterium, especially *Helicobacter pylori*, *Helicobacter hepaticus* or *Mycobacterium tuberculoses* or *Campylobacter pylori*; and it is preferred that the two epitopes are epitopes of a urease and a heat shock protein, preferably Hsp60, of an alkylhydroperoxide-reductase, preferably of the 25kDa protein, the 20kDa-protein (3-dehydro-quinase, type II), of the 16.9 kDA-protein (neutrophil-activating protein) or of the 38kDa-protein (fructose-bisphosphate adolase). *See* Specification page 2, pgh. 1.

With respect to independent claim 77, Applicant notes that claim 77 does not recite the claim language "an epitope of a first antigen" or "an epitope of a second antigen." Rather, claim 77 recites "ß-urease or a fragment thereof" as the epitope to which the first monoclonal antibody of the claim method specifically binds, and "the 26kDa-antigen or a fragment thereof" or "Hsp60 or a fragmen

thereof," as the epitope to which the recited monoclonal antibody specifically binds.

Thus, contrary to the Examiner's contention, undue experimentation is not necessary to practice the method of claim 54-91. Those of skill in the art are clearly capable of determining if a particular epitope shows a structure after intestinal passage that corresponds to a native structure through tests know to those of ordinary skill, including those described. Accordingly, Applicant respectfully submits that the Examiner's rejection of these claims under 35 U.S.C. 112, first paragraph, should with reconsidered and withdrawn.

III. Rejection of Claims 54-91 under 35 U.S.C. 112, second paragraph

The Examiner's rejection of claims 1-4 and 13-14 under 35 U.S.C. 112, second paragraph, has been maintained as applied to newly submitted claims 54-91, as being vague and indefinite in the recitation of "derivative." Citing Dorlands Medical Dictionary, 27th Edition, 1988, the Examiner contends that a "derivative" is a substance derived from another substance "either directly or by modification," and thus argues that the degree that substance can be modified and still remain under the scope of a derivative simply cannot be determined by one of skill in the art. Applicant respectfully disagrees.

Applicant submits that the "derivative" recited in independent claims 54 and 77 are those that specifically bind an epitope . . . which shows at least with some mammals a structure after intestinal passage that corresponds to the nature structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism, an extract or lysate thereof, a protein therefrom, a fragment thereof or a synthetic peptide, etc, as recited in independent claims 54 and 77. Given the foregoing arguments regarding Applicant's enabling disclosure in support of the term "epitope," it is respectfully submitted that with respect to the term "derivative," applicant has particularly pointed out and distinctly claimed the invention of claims 54-91 in accordance with 35 U.S.C. 112, second paragraph. Accordingly, Applicant respectfully submits that the Examiner's rejection of claims 54-91 should be reconsidered and withdrawn.

IV. Claim Rejections Under 35 U.S.C. 102(b)

The Examiner rejection of claims 1-4 under 35 U.S.C. 102(b) as being anticipated by newly submitted claims 54-57, 74 and 76 has been maintained, on the basis that the Applicant's claim of priority to PCT/EP/99/08212 filed October 29, 1999, EP 98 120687.3 filed November 6, 1998 and EP 98 120517.2 filed October 29, 1998 has not been properly set forth by way of either a statement in the specification or an Application Data Sheet. Pursuant to MPEP § 2011.11, Applicant submits herewith an Application Data Sheet which identifies the claimed priorities. As noted in MPEP § 2011.11, "if an applicant includes a benefit claim in the application but not in the manner specified by 37 C.F.R. 1.78(a) (e.g. if the claim is included in an oath or declaration or the application transmittal letter) within the time period specified in 37 C.F.R. 1.78(a)" (i.e. during the pendency of the application, and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application), "the Office will not require a petition under 37 C.F.R. 1.17(t) to correct the claim if the information concerning the claim was recognized by the Office as shown by its inclusion on the filing receipt. As shown in the enclosed Fee Transmittal Form, which was filed with the application on April 21, 2001, Applicant has clearly identified this application as a continuation of PCT Ser. NO. EP99/08212 filed October 29, 1999 which claims benefit of EP Ser. No. 98 120517.2 filed October 29, 1998 and EP Ser. No. 98 120687.3 filed November 6, 1998. The priority data is likewise set forth on the filing receipt issued on September 6, 2001, and in Applicant's Preliminary Amendment filed on January 7, 2001. As, therefore, the priority claim is valid, Larka cannot be an anticipating reference. Nevertheless, Applicant takes this opportunity to note that, as has been outline in the specification and in Applicant's prior responses, Larka unambiguously states that monoclonal antibodies are not useful for a method as claimed in the present application and therefore clearly teaches away from the present invention.

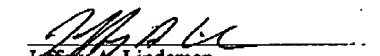
For these reasons, it is respectfully submitted that the rejection of claims 54-57, 74 and 76 under 35 U.S.C. 102(b) should be reconsidered and withdrawn.

Docket No. 32034-1000

IV. Conclusion

Having responded to all rejections and objections set forth in the outstanding Office Action, it is submitted that claims 54-91 are now in condition for allowance. An early and favorable Notice of Allowance is respectfully solicited. In the event that the Examiner is of the opinion that a brief telephone or personal interview will facilitate allowance of one or more of the above claims, the Examiner is courteously requested to contact Applicant's undersigned representative.

Respectfully submitted,



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Enclosures: Application Data Sheet
Official Filing Receipt
Fee Transmittal Form dated 4/21/2001
Budapest Treaty Deposit Receipt (4)

Date: November 2, 2004